Long-Acting LH-RH Agonist Depot (Leuprolide Acetate) for Prostate Cancer

Speaker: Robert C. Tyler, MD, Director of Clinical Research, Atrix Laboratories, Inc., Fort Collins, Colorado.

A new six-month subcutaneous (SC) depot of leuprolide acetate (Eligard®, Atrix Laboratories, Inc.), a synthetic luteinizing hormone–releasing hormone (LH-RH) agonist, consistently produced and maintained safe and effective serum testosterone suppression. Total serum testosterone concentrations were well below the medical castrate level of less than 50 ng/dl in adult men with prostate cancer.

Because treatment strategies to increase symptom-free survival in patients with advanced disease focus on testosterone suppression to ameliorate symptoms and control disease, a multicenter, open-label study was designed to assess the safety, efficacy, and pharmacokinetics of leuprolide acetate. A total of 111 patients received two SC injections of leuprolide depot 45 mg at 0 and six months over a 12-month period. Safety and efficacy, as measured by testosterone suppression and prostate-specific antigen (PSA) levels, were evaluated.

Of the 111 patients, 103 (93%) completed the 12-month study. Overall, mean and median times to castrate suppression were 21.2 and 21 days, respectively. At the completion of the study, 99% of patients had testosterone concentrations that were below the medical castrate level. At 12 months, mean PSA levels decreased by 97%, from 39.8 ± 21.5 ng/ml at baseline, to 1.2 ± 0.3 ng/ml. There were no clinically significant flare reactions. The most common treatment-related adverse drug event (ADE) was mild-to-moderate hot flashes.

Bisphosphonic Acid Compound (Zoledronic Acid) for Bone Metastases in Hormone-Refractory Prostate Cancer

Speaker: Charles Metzger, MD, Urologist, Citrus Valley Urologic Medical Group, Glendora, California.

Zoledronic acid (Zometa®, Novartis), a bisphosphonic acid that inhibits osteoclastic bone reabsorption, is well known for reducing skeletal complications of bone metastases in men with hormone-refractory prostate cancer. This agent is effective in increasing bone mineral density in hormone-sensitive prostate cancer patients with bone metastases.

A prospective, open-label, multicenter clinical trial involved 221 men with advanced prostate cancer and documented bone metastases who were already receiving or just beginning hormonal therapy. The men received zoledronic acid 4 mg as a single 15-minute intravenous (IV) infusion every three weeks, for a maximum of 16 infusions. The primary endpoint of the study was the percentage of change from baseline of the lumbar (L) spine bone mineral density, measured at L2 to L4. Secondary endpoints included bone mineral density of the hip; changes in N-telopeptide and in bone-specific alkaline phosphatase, which are known markers of bone remodeling; the time to the first skeletal event; and safety.

A total of 202 evaluable patients were in the intent-to-treat (ITT) group for efficacy analysis. Overall, there was a mean increase of 7.7% in bone mineral density in the lumbar spine at one year. Hip bone mineral density also increased by 3.6% at one year. Both N-telopeptide and bone-specific alkaline phosphatase decreased significantly from baseline to the final patient visit (\(P < .001\)). A single skeletal event was reported in 8.9% of the patients, and 3% of the patients had multiple skeletal events.

In general, zoledronic acid was safe and well tolerated. As expected, the most common ADEs were arthralgia, nausea, fatigue, back pain, bone pain, and anemia.

Alprostadil Urethral Suppository for Erectile Dysfunction After Radical Prostatectomy

Speaker: Craig Zippe, MD, Staff Surgeon, Section of Urologic Oncology, and Co-Director, Prostate Center and Center for Advanced Research in Human Reproduction, Infertility, and Sexual Function, The Cleveland Clinic, Cleveland, Ohio.

Dr. Prescott is a medical, health, and science writer based in San Diego, California, and a former medical microbiologist and clinical pathologist for the World Health Organization.
The early use of an alprostadil urethral suppository (Muse®, Vivus, Inc.) in men following bilateral nerve-sparing radical prostatectomy appears to facilitate a rapid return to and a high rate of early recovery of normal sexual function.

Ninety-one men who had undergone the procedure participated in a trial to determine whether early, frequent Muse® treatment, at least three times weekly, would speed the recovery time of sexual function. Fifty-six patients received Muse® 125 mcg at least three times a week for six weeks. The treatment was started during the first month after surgery. At six weeks, patients received either 250 mcg at least three times a week, or they continued to take 125 mcg, depending on their tolerability, for another four months or more. The control group consisted of 35 men who refused treatment postoperatively, except for erectogenic aids when sexual intercourse was attempted.

Overall, 28 of 38 evaluable patients who received the study drug (73%) were able to undergo successful vaginal intercourse, with a corresponding satisfaction rate of 67% for the patients’ sexual partners. In addition, 55% of these men reported the recovery of spontaneous erections sufficient for vaginal intercourse after six months of early use of Muse®. Eighteen of the 56 Muse® patients dropped out of the study, citing insufficient erections (50%), reduced sexual interest (28%), or pain and burning associated with the product (22%).

In the control group, 13 of the 35 men reported some degree of success; four reported a return of spontaneous erections sufficient for intercourse without adjuvant treatment. Another nine men reported that they had the ability to perform successful vaginal intercourse but required adjuvant erectogenic aids, including Muse®.

Lidocaine Jelly for Penile Aching Induced by Muse®

Speaker: James K. Dow, MD, Urologist, Urology Section, Veterans Administration Northern California Health Center System, Martinez, California.

Although a sterile bacteriostatic surgical lubricant (Surgilube®, AstraZeneca) and 2% lidocaine HCl (Xylocaine® viscos, AstraZeneca) can provide improved quality of delivery of intraurethral alprostadil (Muse®, Vivus, Inc.) for the management of erectile dysfunction (ED), only a combination treatment with lidocaine jelly has proved effective in eliminating Muse®-induced penile aching.

A total of 74 men with organic ED who responded favorably to a three-month period of Muse® therapy alone but who complained of penile aching were selected for a comparison of 2% lidocaine jelly and Surgilube® in combination with Muse® for the reduction of penile aching. The patients were randomly assigned to one of two groups; 24 patients received Surgilube®, and 50 men received 2% lidocaine jelly. Both preparations were applied to the Muse® applicator stem before insertion into the urethra.

After six months of treatment, the outcome variables assessed included the frequency of episodes of penile aching, the Erection Quality Scale, dual activity as a selective pain inhibitor and erection enhancer, Patient Global Impression of impotence-related quality of life, quality of drug delivery, general improvement with Muse®, and frequency of side effects. Overall, 98% (49/50) of the patients reported complete disappearance of penile aching with 2% lidocaine jelly; only 4% of patients (1 of 24) who received Surgilube® experienced relief. Furthermore, 33% of men (17 of 50) in the combination treatment group with lidocaine stated that their erection quality was significantly improved, in contrast to 8% of patients (2 of 24) in the Surgilube® group.

All of the men who received lidocaine with Muse® expressed improved sexual satisfaction, psychological benefits, and impotence-related quality of life. Both preparations equally provided an enhanced delivery quality of Muse®, and neither product was associated with any adverse reactions.

Vardenafil for Erectile Dysfunction Irrespective of Prior Sildenafil Use

Speaker: William G. Moseley, MD, Medical Director, San Diego Uro-Research, San Diego, California.

Vardenafil (Levitra®, Bayer/GlaxoSmithKline), a new anti-impotence agent, provided clinically significant, sustained improvement in erectile function over a two-year period in men with erectile dysfunction (ED), whether or not they had previously used the original anti-impotence drug sildenafil (Viagra®, Pfizer).

In a double-blind, multicenter, randomized trial, 1,020 men with ED were randomly assigned to take oral vardenafil 10 or 20 mg, as needed, over 52 weeks. A total of 755 men (74%) completed the full 52-week treatment period; 566 men from 57 centers in 10 countries continued to receive double-blind vardenafil for an additional 52 weeks. In this group of patients, 272 men were receiving vardenafil 10 mg and 292 men were receiving a 20-mg dose. At the baseline evaluation, patients in both groups had moderate ED (2.2 and 2.3, respectively). In addition, 56% of the patients in the 10-mg group and 63% of those in the 20-mg group had taken sildenafil before.

Efficacy was defined as the mean per-patient success rate of vaginal penetration, based on the Sexual Encounter Profile Diary Question 2 (SEPQ2), a completion of intercourse (SEPQ3), and satisfaction with the hardness of erections over the past four treatment weeks. These parameters were examined retrospectively in the intent-to-treat population, which was stratified according to prior sildenafil use.

In general, vardenafil elicited similar mean results for each patient’s SEPQ2 and SEPQ3 success rates, erection improvement, and satisfaction with the hardness of erections, irrespective of their earlier use of sildenafil. For example, at baseline, the SEPQ2 success rates were 48.2% in the vardenafil 10-mg patients and 47.1% in the vardenafil 20-mg patients. At the end of the study, the SEPQ2 success rates were 87.2% and 90.1%, respectively, in sildenafil-naive patients and 85% and 83%, respectively, in patients with prior exposure to sildenafil. Global assessments of overall erectile function were 91% and 88.9%, respectively, in sildenafil-naive patients and 90% and 94%, respectively, in patients with prior sildenafil use.

Tadalafil, a Long-Acting Anti-impotence Drug, for Erectile Dysfunction

Speaker: Ridwan Shabsigh, MD, Associate Professor of Urology, Urologic Surgery, and Director, New York Center for

Results from a randomized, double-blind, placebo-controlled study showed that tadalafil (Cialis®, Eli Lilly) 10 and 20 mg administered to men with erectile dysfunction (ED) significantly improved their erectile ability compared with placebo. Assessments were based on mean per-patient percentages of sexual attempts that resulted in successful completion of intercourse when sexual activity occurred 24 or 36 hours after they took the study drug.

A phase 3 clinical trial involving 483 men, who were at least 18 years of age with a minimum of three months’ history of ED, was conducted in the U.S. The patients were randomly divided into groups according to the combination of study treatment, consisting of placebo, tadalafil 10 mg, and tadalafil 20 mg.

The study consisted of (1) a four-week run-in phase without medication; (2) a two- to four-week equilibration phase with dosing, as needed, before sexual activity, but not more frequently than once a day; (3) a four- to six-week assessment phase with four doses of medication, each followed by a sexual intercourse attempt at 24 or 36 hours; and (4) a six-month, open-label extension phase of active medication. Efficacy was measured as the mean per-patient percentage of successful intercourse attempts, based on the Sexual Encounter Profile Diary Question 3 (SEPQ3).

Of the 483 men enrolled, 435 men completed the equilibration and assessment phases of the study; 144 received placebo, 145 received tadalafil 10 mg, and 146 received tadalafil 20 mg. Tadalafil in 10- and 20-mg doses was superior to placebo in the mean per-patient percentage of successful intercourse attempts at 24 hours (55.8 and 67.3%, respectively, compared with 41.8% receiving placebo) and at 36 hours (56.2% and 61.9%, respectively, compared with 32.8% receiving placebo).

The significant improvement in erectile function, which resulted in a greater percentage of successful sexual intercourse attempts, was further corroborated by patients’ increased post-dose satisfaction with the hardness of erections and their overall satisfaction with tadalafil compared with placebo at each of the pre-assigned time periods 24 or 36 hours after they took the dose.

**Extended-Release Muscarinic Agonist (Tolterodine) for Overactive Bladder**

**Speaker:** Jay M. Young, MD, Medical Director, South Orange County Medical Research Center, Laguna Woods, California.

Patients with overactive bladder who received extended-release (ER) tolterodine tartrate (Detrol® LA, Pharmacia) experienced significantly improved perceptions of urinary urgency and bladder condition, compared with patients who took placebo.

To fully evaluate the benefits of tolterodine treatment, investigators randomly assigned 1,015 patients with urinary frequency (defined as more than eight micturitions every 24 hours) and incontinence (defined as more than five episodes per week) to receive tolterodine ER 4 mg or placebo once daily for 12 weeks. A three-point ordered categorical scale was used to assess patients’ perceptions of urgency and bladder condition at the baseline evaluation, and a six-point scale was used to assess their perceptions at the 12th week.

At 12 weeks, 198 patients (39%) taking tolterodine ER and 132 patients (25%) taking placebo reported improved perceptions of urgency. The percentage of patients who reported that they were able to complete a task before needing to void rose from 6% to 30%—a fivefold increase—in the patients given tolterodine ER compared with a difference from 7% to 16%—a two-fold increase—in the placebo group. The number of patients who reported that they were unable to hold their urine declined by 54% in the tolterodine-treated group and by 27% in the placebo group. In the tolterodine group, 58% of patients had improved perceptions of their bladder condition, compared with 43% of the patients who received placebo.

**Solifenacin, an Oral Antimuscarinic Agent for Overactive Bladder**

**Speaker:** Paul F. Siami, MD, Medical Director, Wellborn Clinic, Evansville, Indiana.

In multiple trials, solifenacin succinate (Vesicare®, Yamanouchi), a new once-daily, oral selective muscarine receptor antagonist, provided statistically significant reductions in quantified urgency episodes in patients with overactive bladder. This is the first antimuscarinic agent for which such results have been reported.

These conclusions were reached from the pooled data of four 12-week, randomized, placebo-controlled phase 3 clinical trials that assessed the efficacy, safety, and tolerability of solifenacin in 3,032 patients. The patients were randomly selected to receive treatment, and 2,848 patients were available for statistical analysis. Of this latter group of patients, 2,823 individuals reported urgency at the baseline evaluation; 1,124 received placebo; 548 received solifenacin 5 mg; and 1,151 received solifenacin 10 mg. This group of patients, encompassing all three treatments, had a mean of 5.9 to 6.3 urgency episodes a day and approximately 12 micturitions per day.

Statistically significant reductions of 50% or more in the mean number of daily urgency episodes were reported by 62% of patients taking solifenacin 5 mg, by 66% of those taking solifenacin 10 mg, and by 44% of those taking placebo, compared with concentrations of whichever study drug was used. The changes from baseline to endpoint in the mean number of urgency episodes per 24 hours were ~2.9 for patients taking solifenacin 5 mg, ~3.4 for those taking solifenacin 10 mg, and ~2.0 for those taking placebo.

Most of the anticholinergic side effects were classified as mild to moderate. The most commonly reported ADE was dry mouth, reported by 28% of patients receiving solifenacin 10 mg, by 11% of those receiving solifenacin 5 mg, and by 4% of those receiving placebo.

**FloSeal® Gelatin Matrix for Tubeless Percutaneous Nephrolithotomy**

**Speaker:** Isaac Kim, MD, Clinical Endourology Fellow and Clinical Instructor in Laparoscopic and Endourologic Procedures, Department of Urology, University of California at Irvine, Medical Center, Irvine, California.

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Following successful percutaneous nephrolithotomy (PCNL), a high-viscosity hemostatic gelatin matrix (FloSeal® Matrix Hemostatic Sealant, Baxter), achieved rapid hemostasis and sealing of the nephrostomy tract. This sealant, which is composed of a combination of specially engineered collagen-derived particles and topical thrombin, negated the need for tube or suture placement and helped to shorten the length of hospitalization.

Eight patients who were treated with FloSeal® were compared with eight patients who underwent single-access, standard PCNL. In the FloSeal®-treated patients, after fluoroscopy and endoscopy confirmed that the patients were free of stones, a 260-cm exchange guide wire was passed through the urethra and was retrieved through the flank. An occlusion balloon catheter was passed into the collecting system, and the balloon was inflated under endoscopic control until it occluded entry into the renal collecting system. A syringe of FloSeal® with a laparoscopic applicator was injected while the applicator and the nephrostomy sheath were removed together simultaneously. A Foley catheter was placed, and the skin closed with a topical adhesive, 2-octyl cyanoacrylate (Derma-bond, Ethicon, Johnson & Johnson). The Foley catheter was removed the next morning.

Preoperative, intraoperative, and postoperative results were compared in the two treatment groups of patients. Intraoperative and postoperative findings were similar with regard to operative time, estimated blood loss, change in hematocrit values, and analog pain score. The FloSeal® patients tended to have shorter hospital stays (29 hours) than the patients in the standard PCNL group (49 hours).

A randomized, prospective trial is planned.